Safety and long-term efficacy of fractional CO_2 laser treatment in women suffering from genitourinary syndrome of menopause

Abstract

Objectives: To evaluate the safety and long-term efficacy of fractional CO_2 laser treatment in reducing the severity of symptoms of genitourinary syndrome of menopause (GSM) in menopausal women.

Study Design: 102 women presenting with symptomatic GSM were treated with the fractional CO_2 laser (MonaLisa Touch, DEKA) system across a series of treatments delivered at intervals of six or more weeks. The Australian Pelvic Floor Questionnaire was used to gather data on sexual function and side-effects at three time-points across the study period (prospective panel design study). Wilcoxon signed-rank tests were used to detect statistically and clinically significant changes in sexual function and side-effects occurring from pre- to post-treatment. The primary outcome of this study was an improvement of the symptoms of GSM. The secondary outcome included bladder function and prolapse symptoms.

Results: A total of 102 women suffering from moderate to severe GSM were recruited. Eighty-four percent experienced significant improvement in their symptoms after CO_2 laser treatment. Scores on measures of sexual function, dyspareunia, and bothersomeness of sexual issues were improved from pre-treatment to long-term (12-24 month) follow-up. Furthermore, there were improvements on measures of bladder function (P=.001), prolapse (P=.001), vaginal sensation (P=.001), vaginal lubrication

(P< .001) and urge incontinence (P=.003) from the pre-treatment assessment to the second assessment (i.e. after the third treatment).

Conclusions: In this study, fractional microablative CO_2 laser treatment was associated with an improvement in symptoms of GSM and sexual function.

Keywords: Genitourinary syndrome of menopause, menopause, fractional CO_2 laser, sexual function, bladder control

Introduction

Life expectancy for women has increased significantly during the past century and many women will now spend more than one third of their lives in menopause[1,2]. Many of these postmenopausal women, who expect to maintain good health and a high quality of life into their postmenopausal years, consider sexual health and relationship satisfaction to be of paramount importance.

The sexual health of postmenopausal women can be undermined by the progressive ageing of the body, as well as by genitourinary syndrome of menopause (GSM)[3]. GSM, previously known as atrophic vaginitis, is a multifaceted oestrogen-dependent condition which often occurs as a manifestation of menopause[4]. The fall in oestrogen resulting from menopause causes the vaginal epithelium to become thin and pale[1], lose vascularity, collagen fibres, leading to decreased engorgement, lubrication, and reduced elasticity. Vaginal smears of patients suffering from GSM demonstrate a unique morphology whereby superficial cells are scant and there is an increase in intermediate and parabasal cells in hypoestrogenemic conditions, which, along with decreased glycogen-rich cells, promotes increased vaginal pH[5]. These conditions increase the risk of developing symptoms such as dryness, burning, itching, irritation, abnormal discharge, recurrent thrush and dyspareunia, which are likely to cause an altered response to sexual stimuli[4]. This discomfort associated with intercourse often leads to a vicious cycle of decreased desire, arousal, orgasm and frequency of coitus, resulting in loss of self-confidence and depression throughout the pre- and postmenopausal stages.[6]

It is estimated that about 8-22% of premenopausal women and 40-57% of postmenopausal women experience symptoms resulting from GSM[7]. However, only 1 in 5 women experiencing these symptoms will consult a physician on issues related to GSM[1]. Current therapies for GSM include hormonal therapy with oestrogen alone (ET) and oestrogen-progestin therapy (EPT). Whilst these therapies may be effective in increasing vaginal lubrication and reducing dyspareunia, they have not been shown to consistently increase sexual desire or activity[8].

Due to embryological origin, the lower one third of the vagina (like the urethra and bladder) has fewer oestrogen receptors than the upper two thirds, which may impact the effect of hormonal therapy on the lower third[7,9]. For this reason, hormonal therapy is not particularly effective as a treatment for superficial dyspareunia. In addition, a subgroup of women demonstrates contraindications to hormonal therapy or experiences relapse shortly after treatment[8]. The rate of medical adherence to this line of therapy is quite variable (52-74%) mainly due to safety concerns, inconvenience, and inadequate symptom relief from available treatments[10,11]. There is a lack of long-term safety data for vaginal hormonal therapy and the important question of whether it is safe to use local oestrogen treatment in cancer survivors remains unanswered[2]. Regardless, patients diagnosed with breast cancer are often reluctant to use oestrogen treatment. Therefore, the need to consider non-pharmacological approaches is essential.

Fractional micro-ablative CO_2 laser represents one potential non-pharmacological approach to GSM. Broadly speaking, laser treatments employ heat to improve the collagen structure of tissue[12]. Fractional micro-ablative CO_2 laser achieves its effects by

thermally altering only a fraction of the epidermal and/or dermal architecture, leaving intervening areas unaltered[13]. These intact areas allow for rapid healing of the tissue[13]. Modern fractional microablative CO_2 lasers incorporate trains of very short high peak power pulses with long interpulse intervals; this modification allows for cleaner incision or ablation with less charring because each pulse is shorter than the thermal relaxation time of the target tissue, so that optimum ablation and heat deposition is achieved with minimal heat build-up in the adjacent tissue[14].

Fractional micro-ablative CO_2 has proved to be safe in remodelling tissue properties of many body regions, such as the skin of the face, neck and chest, and has the ability to produce new collagen and elastic fibres[15]. Within the atrophic vagina, fractional micro-ablative CO_2 treatment has been reported to produce a thicker epithelium along with larger diameter epithelial cells rich in glycogen[16]. Further, this therapy has been shown to increase *Lactobacillus* and reduce vaginal pH[17].

To date, a handful of studies have investigated the short-term effects of fractional CO_2 laser as a treatment for GSM (Table 1). These studies have demonstrated short-term improvements in Vaginal Health Index (VHI) scores, vaginal dryness, burning, itching, dyspareunia and dysuria, generally in postmenopausal samples.

[Insert Table 1]

The pilot study of 50 women conducted by Salvatore. et al.[18] demonstrated that treatment with fractional CO_2 was feasible, safe and resulted in significant improvement of symptoms related to atrophy at 12 weeks' follow-up. These outcomes are reported to

significantly improvement overall sexual satisfaction and quality of life[18]. However, no study has assessed the long-term efficacy of fractional CO_2 laser treatment. The purpose of this study was to investigate the safety, feasibility and long-term efficacy (12-24 months) of fractional micro-ablative CO_2 treatment in a cohort of postmenopausal women suffering dyspareunia and/or other symptoms due to GSM. The primary objective focussed on improvement of GSM symptoms and sexual satisfaction. As a secondary end-point, we investigated any potential side-effects associated with the treatment, with a focus on bladder function symptoms of prolapse.

Materials and methods

Women with symptoms of genitourinary syndrome of menopause (GSM) who were not responding to or not able to take conventional treatments (such as oestrogen therapy for postmenopausal women) were recruited to the study and underwent vaginal treatment with fractional CO_2 laser.

Inclusion criteria included postmenopausal women aged between 51 and 86 years, and complaint of at least one of the following GSM symptoms: (1) vaginal dryness, and/or (2) dyspareunia. Exclusion criteria included unexplained bleeding, abnormal pap-smear, active genital infections or any kind of active cancer within the urogenital area. Patients undergoing any concomitant treatment throughout the study period were excluded.

At the first consultation, all the women were asked to provide written informed consent for their clinical data to be collected for the purpose of clinical quality study, and where applicable, for scientific presentation and/or publications. They were also asked to complete a validated interviewer-administered pelvic floor questionnaire (the

Australian Pelvic Floor Questionnaire)[19] which integrates bladder, bowel, sexual function, pelvic organ prolapse, severity, bothersomeness and condition-specific quality of life, on a scale of 0 to 3 (see attached survey). A gynecologist (FBW) performed a colposcopy and graded the atrophy according to elasticity, fluid volume, epithelial integrity and moisture as per Bachmann to define atrophy on a modified four-point scale (not atrophic, mild, moderate and severe atrophy).

For analysis of treatment outcomes, intensity of GSM symptoms (vaginal dryness, vaginal dyspareunia, vaginal tightness, prolapse symptoms, bladder function and urge and stress incontinence) was recorded using measures of frequency and severity. Questionnaires were completed anonymously. Nurses collected each questionnaire after completion and labelled it using a random computer-generated enrolment number. Clinical data and the questionnaire were collected at baseline before the first treatment (T1), between 2 to 4 months from initial treatment (T2), and between 12 to 24 months after the initial laser treatment (T3). The study received Human Research Ethics approval from Bellberry Limited (Application ID: 2016-04-293). Patients were not compensated for participation in this study.

Study protocol

Prior to laser treatment, all patients underwent colposcopy to stage and confirm atrophic vaginitis and to exclude other underlying pathology such as vulvar intraepithelial neoplasia (VIN) and lichen sclerosus. Pelvic ultrasound was carried out at baseline to assess and record endometrial thickness. Patients with a past medical history of genital herpes were given prophylactic antiviral medication. Each participant was treated with the fractional microablative MonaLisa Touch CO_2 laser system (SmartXide2 V_2LR ,

DEKA, Italy) with the following settings: power 30 watts, dwell time 1,000 µs, DOT spacing 1,000 µm, SmartStak parameter 2, and D- pulse mode. The laser beam was emitted after the vaginal probe was inserted to the top of the vaginal canal, then rotated and withdrawn in order to provide complete 360° coverage of the vaginal wall. The vestibule and fourchette were treated with a 90°probe, with the following settings: power 20 watts, dwell time 1,000 µs, DOT spacing 1,000 µm, SmartStak parameter 1, and D- pulse mode.

A silicon-based balm was used post-procedure to enhance wound healing and aid hydration of the skin. The balm was not used vaginally; rather, it was applied to the fourchette of the vagina. The balm contained a combination of physiologic lipids and botanical sterols and has been previously shown to reduce post-operative swelling, aid healing and reduce the risk infection following laser treatment [20].

Each patient received three fractional CO_2 vaginal laser treatments at intervals of six or more weeks. Follow-up was approximately 12 months after the initial treatment. The procedure was performed by one gynaecologist. Participants did not require any specific analgesia or anaesthesia. They were advised to avoid vaginal intercourse, bathing, and using the bath for at least 5 days after each laser application, so as to allow tissue healing.

Statistical analysis

Based on the study by Pitsouni et al. [21] a sample size of 47 participants would be required to achieve 5% significance, 90% power and a hypothetical effect size of 0.5 (medium effect). With the expectation that there would be ~50% attrition from the

time of recruitment to follow-up, we needed a minimum of 94 patients enrolled in the study. Wilcoxon signed-rank tests were used to detect any statistically and clinically significant differences occurring from pre- to post-treatment. Statistical significance was set at 0.05. Data were analyzed using IBM SPSS software, version 21.0 (IBM, New York, NY).

Results

In this study, we recruited 102 postmenopausal women experiencing symptoms of GSM with an age ranging from 51 to 86 (M = 61.00; SD = 7.00). All the cases were postmenopausal.

Among women in study, common reasons given for discontinuing oestrogen therapy include (i) local side-effects (e.g. irritation, a sensation of burning), (ii) a desire to find out whether climacteric symptoms have ended, (iii) fear of breast cancer and (iv) fear of thrombo-embolism.

Changes in severity of GSM symptoms

Approximately 84% of the patients who suffered from moderate or severe GSM experienced an improvement in symptoms, moving into the ‘mild’ or ‘not atrophic’ categories following treatment (Figure 1). A Wilcoxon signed-rank test revealed a statistically significant improvement in GSM symptoms following participation in treatment, z = -7.75, $p < .001$, with a large effect size (r = .57). The median severity score decreased from pre-treatment (Md = 2) to post-treatment (Md = 0).

[Insert Figure 1 here]

Sexual Function

Median scores on sexual function variables at pre-treatment (T1), after third treatment (T2; 2-4 months after initial treatment), and at 12-24 month follow-up (T3) are shown in Table 2. Due to patient attrition, sample sizes are reported for each time-point. There were statistically significant improvements for all variables assessed, including scores on sexual function, painful intercourse, and other sexual issues including vaginal dryness and reduced libido.

[Insert Table 2 here]

There was an overall reduction in the participants' sexual dysfunction scores from T1 to T2, with an increase in the number of patients reporting "normal" sexual functioning from 24.1% at T1 to 58.4% at T2 (Figure 2). This trend remained stable (63.6%) at T3 (12-24 month follow-up). The percentage of participants reporting mild, moderate and severe sexual dysfunction tended downwards from T1 to T3 (insert data?).

[Insert Figure 2 here]

There was an overall improvement in participants' self-reported pain during intercourse (i.e. dyspareunia; Figure 3), with an increase from 13.2% at T1 to 32.1% at T2 in the percentage of participants who self-reported "never" experiencing painful intercourse. The trend remained stable (34.2%) at T3.

[Insert Figure 3 here]

This trend was mirrored by the percentage of participants self-reporting “bother” with sexual intercourse issues (Figure 4).

[Insert Figure 4 here]

Secondary effects

While the focus of the study was on GSM and sexual function, we also investigated several effects of the laser treatment among women with urinary incontinence issues or prolapse. Other variables from the Australian Pelvic Floor Questionnaire were analysed using Wilcoxon’s signed-rank test (Table 3). There were significant improvements from T1 to T2 on indices of prolapse, vaginal sensation, vaginal lubrication, bladder function, and urge incontinence. These improvements were also observed at T3.

[Insert Table 3 here]

We observed complications in a small number of patients. Following treatment, three women experienced post-coital urinary tract infections and two experienced vaginal discharge/infection; all of them required antibiotic treatment. Three women experienced lower pelvic pain for two to three days, and required simple analgesia (such as

ibuprofen). One patient (who had failed to inform us about her past medical history of genital herpes) had a genital herpes breakout following treatment. Finally, two women presented with postmenopausal bleeding following their third laser treatment (at 4 months and 6 months respectively). Investigation of the endometrial thickness revealed and increase in their endometrium from 3mm to 5mm. Their endometrial biopsies were benign. The increase in endometrial thickness may be coincident, or may be related to revitalisation and rejuvenation occurring beyond the vagina following laser treatment.

Discussion

Fractional CO_2 laser treatment has displayed a good safety profile[13,22] though there is a need for larger-scale studies to assess the risk/benefit profile of this treatment in patients with GSM[18]. This study is the first to assess the long-term effects of fractional microablative CO_2 laser treatment on GSM symptoms, sexual function, bladder-related issues, and prolapse in postmenopausal women who had failed to respond to oestrogen therapy. Previous pilot studies of fractional microablative CO_2 laser in GSM patients have tended to adopt the Vaginal Health Index (VHI) and/or a Visual Analogue Scale (VAS) to measure symptom intensity. To the best of our knowledge, this is the first study of its kind to employ the Australian Pelvic Floor Questionnaire, to record changes in general bladder function, sexual function, urge incontinence and prolapse following fractional microablative CO_2 treatment.

In the short term (2-4 months after the initial treatment), we observed significant improvements in sexual function, dyspareunia, sexual issues, bladder function, prolapse symptoms, vaginal sensation and lubrication, and urge incontinence. From baseline to long-term follow-up (between 12 and 24 months), we recorded statistically significant improvements in all above mentioned variables. This indicates that the improvements observed in the short term were maintained at long-term follow-up.

It is likely that these positive effects observed at follow-up in postmenopausal women were due to the alleviation of urogenital symptoms and the restoration of genital tissue viability. Our current data provide evidence for the efficacy of fractional microablative CO_2 laser treatment in improving symptoms associated with GSM and quality of life at short- and long-term follow-up. These results are consistent with those of

Salvatore et al.[18], Filippini & Farinelli[23], Perino et al.[22] Pieralli et al.[24], and Sokol et al.[25]. The size of the cohort within this study adds strength to the findings, and the long-term follow up demonstrates long-term efficacy of this therapy[18,22-25]. To the best of our knowledge, this is the first study of its kind to be completed in Australia.

The high rate of women with improved sexual function as well as the reduction in pain and irritation experienced by patients following intercourse further supports the use of fractional microablative CO_2 laser as a treatment for GSM in postmenopausal women. Specific factors related to sexual function, such as vaginal lubrication and vaginal tightness, improved following treatment. This demonstrates the multi-modal ability of this technique to treat a wide range of symptoms. Although not the primary outcome of this study, the improvement in prolapse symptoms, impaired bladder function, urge and stress incontinence were interesting outcomes of this study. It is possible that fractional microablative CO_2 laser is also improving the general comfort and self-confidence of patients, thus further contributing to their enhanced sexual function.

One limitation of our study was the high attrition rate; participant responses decreased by less than half from the third treatment to the 12-24 month follow-up, making it difficult to be confident in the soundness of comparisons from baseline to the final follow-up. However, we recruited a larger number of participants that previous studies in anticipation of patient attrition during follow-up. Another weakness of this study is the absence of a control group receiving either a placebo or hormonal treatment. However, these data combined with the other short-term studies using fractional CO_2

laser treatment provide evidence to warrant a randomised controlled trial. Furthermore, it would be of interest to extend the use of fractional CO_2 lasers to women with severe contraindications to hormonal treatments, such as cancer survivors who lack long-term safety data for hormonal therapy.

Nevertheless, this study demonstrates that fractional CO_2 laser treatment can provide long-term improvements in the GSM symptoms for postmenopausal women, and these data combined with the other short-term studies using fractional CO_2 laser treatment provide sufficient evidence to warrant a randomised controlled trial. The results of this study are encouraging in that women with age-related GSM who are normally unresponsive to oestrogen therapy experienced noticeable improvements in their sexual function, dyspareunia and the overall severity of symptoms associated with this condition.

In conclusion, the present study demonstrates that fractional micro-ablative CO_2 laser promises to offer an effective, safe and non-invasive treatment alternative for GSM, with improvements in sexual function, reduced symptoms of dyspareunia following intercourse and an overall satisfaction with sexual life in postmenopausal women suffering from GSM. This study adds to the current literature by providing pioneering evidence into the long-term effects of ongoing treatment with fractional microablative CO_2 lasers. The results of this study are encouraging in that they present an alternative treatment to topical estrogen in women who are nonresponsive and/or noncompliant, as well as women who have been advised not to use E2 or those high-risk women who are worried about possible side effects.

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Disclosures

The authors have not conflict of interest. FBW is a preceptor for Monalisa and runs laser workshops for the company. FBW is paid to run these teaching workshops but received no support, financial or otherwise, to run this study.

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Figure legends

Figure 1. Changes in severity of GSM symptoms between pre-treatment (T1; n = 94) and post-treatment assessment (T2; n = 92). Women were scored for GSM symptom severity pre- and post-treatment. Symptom severity was rated in the following categories: not atrophic, mild atrophy, moderate atrophy, or severe atrophy. The percentage of women in each category is shown.

Figure 2. Change in participants' sexual dysfunction scores at pre-treatment (T1; n = 83), after the third treatment (T2; n = 77), and at 12-24 month follow-up (T3; n = 33). Women rated their level of sexual dysfunction in the following categories: normal, mildly affected, moderately affected and severely affected. The percentage of women in each category is shown.

Figure 3. Changes in the frequency of self-reported pain during intercourse at pre-treatment (T1; n = 91), after the third treatment (T2; n = 84), and at 12-24 month follow-up (T3; n = 38). Women rated the frequency of pain during intercourse in the following categories: never, occasionally, frequently, and always. The percentage of women in each category is shown.

Figure 4. Extent to which patients reported that sexual issues were bothering them at pre-treatment (T1; n = 98), after the third treatment (T2; n = 88), and at 12-24 month follow-up (T3; n = 42). Women rated how bothersome sexual issues were according to the following categories: not at all, slightly, moderately or greatly. The percentage of women in each category is shown.

Table legends

Table 1. Summary of results from studies investigating fractional CO_2 laser as a treatment for GSM.

Table 2. Scores on sexual variables at pre-treatment (*T1*), after the third treatment (*T2*), and at the 12-24 month follow-up (*T3*). Changes are represented using Wilcoxon's signed-rank test scores.

Table 3. Description of positive side-effects at pre-treatment (*T1*), after the third treatment (*T2*), and at the 12-24 month follow-up (*T3*).

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